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# Inflammation and blood cells in cardiovascular diseases

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## ABSTRACT

Coronary artery disease (CAD) is still the most important cause of death in developed societies. Atherosclerosis is recognized as a systemic immune inflammatory disease. Inflammation in CAD can be both local and systemic. The main advantage of hematological parameters and indices is that they are relatively inexpensive and therefore common and easy to find in daily clinical practice. In this review, we will try to explain the main hematological parameters and their effects on pathophysiology in patients with atherosclerotic cardiovascular disease.

**Keywords**; Cardiovascular disease, inflammation, white blood cells, red blood cells

## INTRODUCTION

Despite all the advances in diagnosis and treatment at a dizzying pace, coronary artery disease (CAD) is still seen as the most important cause of death in developed societies. Atherosclerosis is the most common cause and is accepted as a systemic immune inflammatory disease.[1] Chronic low-grade inflammation plays a key role in every stage of the atherosclerotic plaque (from the initial stage of the plaque to the complicated stages such as the rupture-thrombus stage). In addition, inflammation is accepted as one cause of diseases such as diabetes, hyperlipidemia and endothelial dysfunction in the etiology of atherosclerosis.[2]

Inflammation in CAD can be both local and systemic. Increased myeloid activity and sympathetic activity lead to the proliferation of stem cells in the bone marrow and induce systemic inflammation.[3] The main advantage of hematological parameters and indices is that they are relatively inexpensive and therefore common and easy to find in daily clinical practice. Almost all the inflammation parameters have been primarily used in malignancy studies and have been found to be a prognostic indicator of negative outcomes.[4,5] Since it has similar pathophysiological factors, it is thought that it can be used in atherosclerotic vascular diseases. They have also proven their diagnostic and prognostic value in many cardiovascular diseases, including heart failure (HF), cardiac arrhythmias, and pulmonary hypertension.

In this review, we will try to explain the main hematological parameters and their effects on pathophysiology in patients with atherosclerotic cardiovascular disease. In recent years, these cells have become increasingly important as they can provide independent information on pathophysiology, risk stratification and optimal management.

## RED BLOOD CELLS (RBC)

While evaluating the outcome of studies, the effect of the diseases on RBCs is searched since it is considered a result of the disease process rather than a cause of the disease. The Red Blood Cell Distribution Width (RDW) index is utilized extensively. RDW is a measure that signifies the variability in the size of red blood cells, thereby indicating their heterogeneity.[6]

Studies show that increased RDW values are associated with adverse outcomes and mortality after coronary intervention in patients with HF, stroke, acute myocardial infarction (AMI), peripheral artery disease (PAD), and also acute coronary syndrome (ACS).[7,8] Lower RDWs are associated with a lower risk of major cardiovascular events in patients with ACS.[9]

Inflammation, increased adrenergic and neuroendocrine system activity, and activation of the renin-angiotensin system seem to cause altered maturation of RBCs, anisocytosis, and an increase in RDW. Oxidative stress is also effective in increasing RDW in acute inflammatory conditions by damaging RBC membranes and causing the bone marrow to release immature RBCs into the peripheral blood.[10]

## WHITE BLOOD CELLS (WBC)

Many studies have demonstrated that leukocytosis seen at presentation in both chronic coronary syndromes and ACS is associated with increased cardiovascular mortality and morbidity (microvascular damage, congestive heart failure, and shock development).

As a result of the studies, it has been shown that using the ratios of each other rather than evaluating WBC individually in the evaluation of CAD and inflammation. (neutrophil-

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lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, etc.)

## Neutrophils

Neutrophils belong to the polymorphonuclear leukocytes family, as they have a segmented nucleus. Neutrophils are the most common among leukocytes. These cells have a relatively short lifespan and contain granules containing highly toxic compounds. The primary task of neutrophils in physiological conditions is to kill harmful microorganisms that enter the body. Neutrophils also have the capacity to phagocytize bacteria killed by released proteases and antimicrobial factors.

The neutrophil-to-lymphocyte ratio (NLR) is easily calculated by dividing the neutrophil count by the lymphocyte count. It is one of the most studied hematological biomarkers that provides prognostic and diagnostic information in CAD. Its role in cardiovascular disease has been extensively studied over the past few years.

A high NLR can be used as an indicator of both the onset and progression of atherosclerosis.[11] It has been investigated as an indicator of mortality and morbidity in both ACS patients and patients undergoing coronary angiography.[4,12] However, it was concluded that it is associated with intra-coronary events (coronary flow velocity, no-reflow, etc.) after percutaneous coronary intervention (PCI).[13] It was concluded that an elevated NLR in patients undergoing coronary artery bypass graft (CABG) was more associated with mortality after CABG.[14] The study conducted also revealed a relationship between NLR and coronary collateral development.[15]

In addition, there are studies claiming that NLR can also be used as a predictor for the development of arrhythmia. It has been shown in studies on the development of atrial fibrillation (AF) both after various operations and after CABG and PCI. In addition, it is also predictive for ventricular arrhythmias.[16] As a matter of fact, in our studies, we have shown that it is a predictor of AF development in patients with COVID-19 disease and after CABG.[17,18] An NLR of patients with acute decompensated HF was associated with frequent decompensation and long-term mortality.19 It has been shown that patients with severe mitral stenosis have a higher NLR compared to patients with moderate and mild aortic stenosis.[20] It was also confirmed that high NLR is an independent indicator of severe rheumatic mitral stenosis.[16]

There is an increasing number of studies showing that NLR can be used to determine the degree and prognosis of the disease in carotid artery disease (CAD). They showed NLR can be used to determine the prognosis after endarterectomy.[21] Studies have shown the relationship between NLR and the incidence, severity, response to treatment and prognosis of PAD.[22-26]

Neutrophils play an important role in the pathophysiology of CAD, given their effect on the instability of atherosclerotic plaques. In the first stage, they penetrate the endothelial cells and become activated when they reach the tunica intima.[27]

It has been hypothesized that the interaction between neutrophils and endothelial tissue causes increased endothelial damage. Severe inflammation is present in cases of ischemic tissue damage in which leukocytes play a key role.[28] Various processes have been suggested, including plaque disruption caused by neutrophil infiltration and increased neutrophil adhesion. It has been shown that neutrophil invasion in atherosclerotic plaque.[29] The plaques can also be more vulnerable by the release of neutrophils, proteolytic enzymes, arachidonic acid derivatives and superoxide radicals. Neutrophils also secrete inflammatory mediators and are associated with an acute inflammatory response to tissue damage.[29] In addition, necrotic core area was positively correlated with lesion size and plaque sensitivity, while neutrophil count was inversely related to smooth muscle cell count and fibrous cap thickness in atherosclerotic lesions.30 Cytokines released from neutrophils regulate vascular tone by blocking nitric oxide synthesis and enhancing endothelin-1 release, and contribute to the development of proliferative vascular lesions by stimulating smooth muscle and interstitial cell proliferation.[31,32]

It may be related to dysfunction of the autonomic nervous system and neutrophil count and thus inflammation. In fact, it has been reported that the distribution of leukocyte subtypes is regulated by the autonomic nervous system. Neutrophils have adrenergic receptors, and the number and function of neutrophils are stimulated by sympathetic nerve endings.[33] Therefore, an imbalance in the autonomic nervous system may play a role in the development and progression of atherosclerosis.[34]

## Lymphocyte

Lymphocytes are cells with a diameter of 8-12 microns, large nuclei, and narrow cytoplasm. There are approximately 2 billion lymphocytes, and millions of them are released into the bloodstream daily. In humans, lymphocytes make up 20-40% of the WBCs in the blood. T cells and B cells provide protective immune responses against various pathogens and form long-lasting immunological memory. To maintain a competent and strong immune system, the peripheral pool of mature lymphocytes is tightly regulated by a careful balance of cell production, survival, death and proliferation.

When evaluating the relationship between CAD-inflammation and lymphocyte, the ratios obtained by dividing 3 different cell numbers by each other were used in the overlaps. NLR, the monocyte-lymphocyte ratio (MLR), and the platelet-lymphocyte ratio (PLR). The work of NLR was mentioned a little above.

The no-reflow phenomenon and its association with negative in-hospital outcomes have been demonstrated in patients undergoing primary PCI for lymphocyte-monocyte ratio (LMR), ST elevation AMI.[35] It has been reported that there may be a relationship between LMR and the severity of CAD and in-stent restenosis after PCI in patients with CAD.[36-38] LMR is an independent risk factor for subclinical CAD.[39] LMR appears to be an independent predictor of mortality in patients with acute pulmonary embolism.[40] LMR is independently associated with a higher risk of mortality in acute HF and aortic dissection.[41,42] In addition, LMR levels can be used to evaluate the severity of CAD.[43]

It has been shown that PLR is correlated with higher overall mortality and morbidity in ACS patients.[44,45] In addition, PLR seems to be helpful in predicting complications after emergency and elective PCI and in selecting risky patient groups.[46,47] The PLR has the ability to predict sub-clinical atherosclerosis, atherosclerosis progression in CAD, and the tendency for carotid stenosis to become symptomatic after carotid interventions with morbidity.48 PLR is associated with PAD and may indicate the degree of atherosclerosis.49 Increased PLR may be a helpful biomarker for severity and survival prognosis in HF patients.[50]

Lymphocytes, which are located in the regulatory pathway of the immune system, are inversely related to inflammation and play a very important role in the atherosclerosis process by regulating the inflammatory response.[51,52] Lymphocytes have an active role in the anti-inflammatory response by increasing the immune response during the systemic stress response and regulating serum levels of catecholamines and cortisol.[53,54] Inflammation contributes to atherosclerosis plaque formation and progression; it is regulated by immune cells, cytokines and other biomedical markers and may increase atherosclerotic plaque progression and CAD development.[13,55] Lymphopenia occurs as a result of physiological stress and the cause of possible mechanisms such as decreased cell production, tissue-level redistribution, or cell apoptosis. With the increase in lymphocyte apoptosis in atherosclerotic plaque, plaque development progresses and destabilization occurs in the plaque.[56,57]

### Monocyte

Monocytes are the largest cells in the blood. They have a diameter ranging from 14 to 20 micrometers. It has cytoplasmic granules and, due to the phagocytic and motile nature of monocytes, its surface has an irregular structure. They are formed in the bone marrow and circulate in the blood for about 1-3 days before migrating to tissues where they differentiate into macrophages or dendritic cells. Monocytes have functions of phagocytosis, antigen presentation, cytokine secretion, tissue repair, and modulating the immune response by influencing other inflammatory cells. When evaluating the relationship between CAD-inflammation and monocytes, LMR and the ratio of monocytes to high-density lipoprotein cholesterol (monocyte-HDL-C ratio, MHR) are often used as indicators in cardiovascular disease studies. The significance of LMR in cardiovascular health was mentioned in the previous section.

Several studies reported that MHR is independently and significantly associated with long-term mortality in patients with ST-segment elevation myocardial infarction (STEMI), as well as with high SYNTAX scores.[58,59] High MHR is associated with the slow flow/no-reflow phenomenon.[60] Studies suggest that a higher MHR is associated with an increased prevalence of CAD, a hogher mortality rate, and the potential for complications in ACS.[60] There are also few studies showing that MHR is independently and significantly associated with the SYNTAX score in patients with chronic coronary syndrome.[61]

Monocyte migration to the arterial wall is considered one of the early events in atherogenesis and persists in all stages of the disease. They migrate to plaque areas with chemotactic stimuli. There are 3 main roles played by monocytes in the progression of atherosclerosis. First, they play a role in the long-term process of initiation and formation of atherosclerotic plaque by going to the plaque site where adhesion occurs. In the subendothelial space, they differentiate into macrophages that take up oxidized LDL via scavenger cells to form foam cells. Second, they are involved in the acute inflammatory phase following destabilization and rupture of the atherosclerotic plaque and acute thrombus formation. It causes thinning of the fibrous cap due to the enzymes that occur with monocyte-platelet interactions. Finally, they play a role in promoting a variety of beneficial or harmful inflammatory processes in the myocardial tissue during the healing process, particularly during the hypoxic phase.[62-64] The resulting reactive oxygen species increase inflammation.[65]

## PLATELETS

Platelets are anuclear and are not amorphous, they have a characteristic discoid shape in their resting state. They originate from megakaryocytes in the bone marrow. Their average lifespan is 7-10 days. It is responsible for initiating the hemostatic mechanisms for repairing the damaged endothelium. Platelets have four main tasks: binding, activation-secretion, aggregation and interaction with coagulation factors. PLR, platelet distribution width (PDW) and mean platelet volume (MPV) are used in studies to evaluate the relationship between CAD-inflammation and the platelet. The work of PLR was mentioned a little above. PDW indicates the changed platelet size. The large number of immature platelets results from increased bone marrow activity during the process known as thrombocytopoiesis. PDW measured at admission is a biomarker that predicts the development of HF in patients with ACS after PCI. It has also been shown to be associated with the severity of CAD. Positive correlations have been reported between a high PDW and a high Gensini score. There are studies showing that PDW can be used in the differentiation of stable and ACS patients and can serve as a useful prognostic factor for mortality in patients after AMI.[4]

MPV is a useful, indirect and easily labeled biomarker of platelet activity. Numerous studies support the association of MPV with adverse cardiac outcomes in patients with CAD. MPV was a strong and independent predictor of impaired reperfusion and mortality in ACS patients undergoing PCI, and has been shown to be associated with the development of restenosis-thrombosis in patients undergoing PCI.[66-71]

An ever-increasing number of data suggests platelets are a population of cells actively involved in atherosclerosis, and that there is also a crucial cross-link between inflammation and thrombosis.[72] Although platelets do not adhere to the vascular endothelium under normal (physiological) conditions, endothelial cell activation or disruption of the endothelial layer leading to a proinflammatory phenotype facilitates platelet adhesion to the vascular wall.[73]

With adhesion, platelets release copious amounts of proinflammatory chemokine that attract circulating leukocytes and facilitate their uptake to the vascular wall.[74] In addition, inflammatory mediators released from activated platelets promote vascular inflammation at lesion sites. It contributes to the progression of atherosclerosis by promoting the aggregation of other platelets and inflammatory cells.[75] In addition, some chemokine help activate angiogenesis. In addition, activated platelets contribute to extracellular matrix degradation and local activation of factors that promote plaque rupture and thrombus formation.[76,77]

## CONCLUSION

It is clear that there is a need for a reliable, accessible, non-invasive and hematological prognostic marker to identify patients with high cardiovascular risk in both primary and secondary prevention in CAD, as well as determining treatment modalities after the disease occurs - predicting complications and mortality. The review presented here has attempted to reflect the complex pathophysiology of CAD. Inflammatory processes play a key role in the development

of atherosclerosis, destabilization of atherosclerotic plaques, and clot formation on the plaque surface. It is reasonable to assume that a better understanding of the multifaceted roles of these hematological cells in the inflammatory processes that occur during atherosclerosis may provide clues for additional targets for diagnostic and/or therapeutic intervention.

## ETHICAL DECLARATIONS

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